# No one remembers when the second team wins: Strategies of rhinovirus immune manipulation

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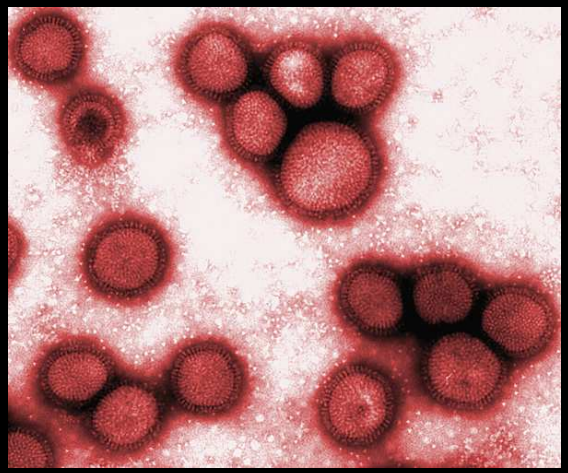
# The sadly neglected rhinoviruses

## Influenza

- One or two types per year
- Potentially deadly
- Lifelong immunity
- Peak in the winter



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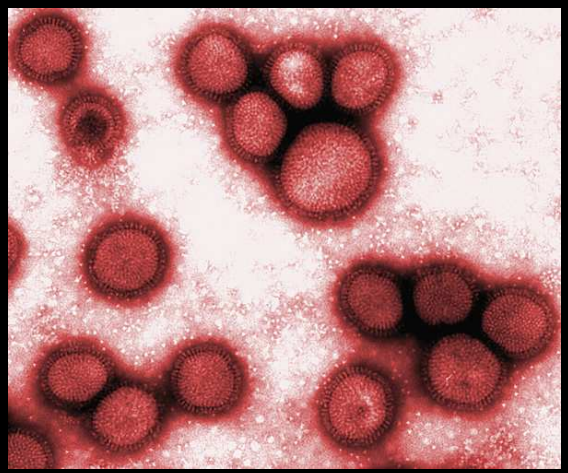

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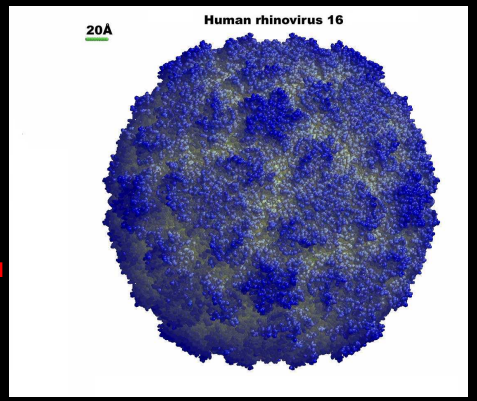
## Rhinovirus

- Over 100 co-circulating serotypes
- Mild infections
- Limited and temporary immunity
- Peak in fall and spring




virology.wisc.edu

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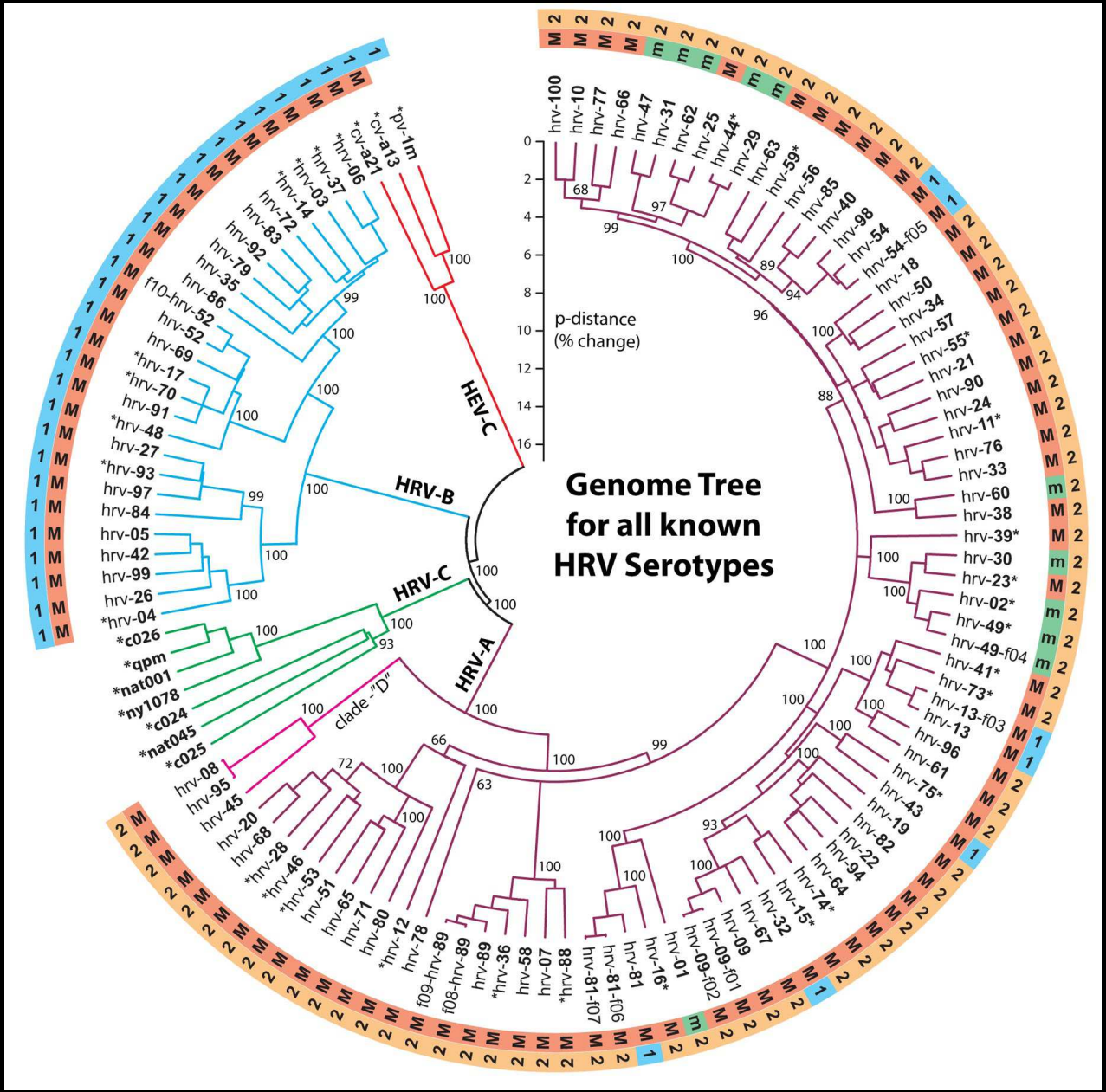
- Why don't we seem to become immune?
- How does the body clear them with both limited pathology and limited immune response?
- Why do we get them primarily in the fall and spring?
- Why are there so many?

# The phylogeny of rhinoviruses




Palmenberg, 2009

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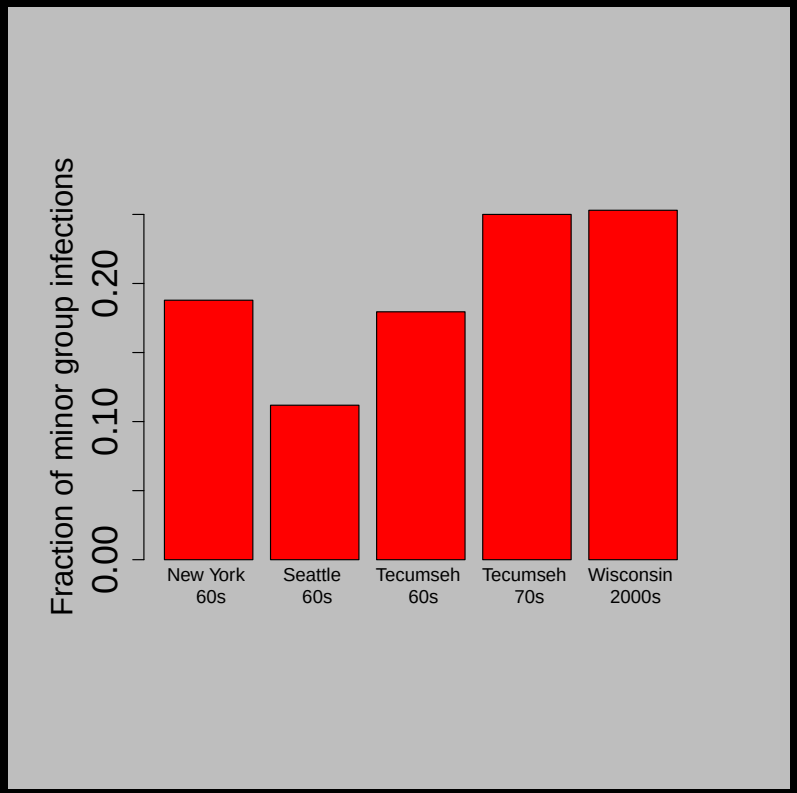
- All of the minor group viruses fall within HRV-A
- The two groups use different cell surface receptors
- Frequency of minor group fairly constant in classic studies



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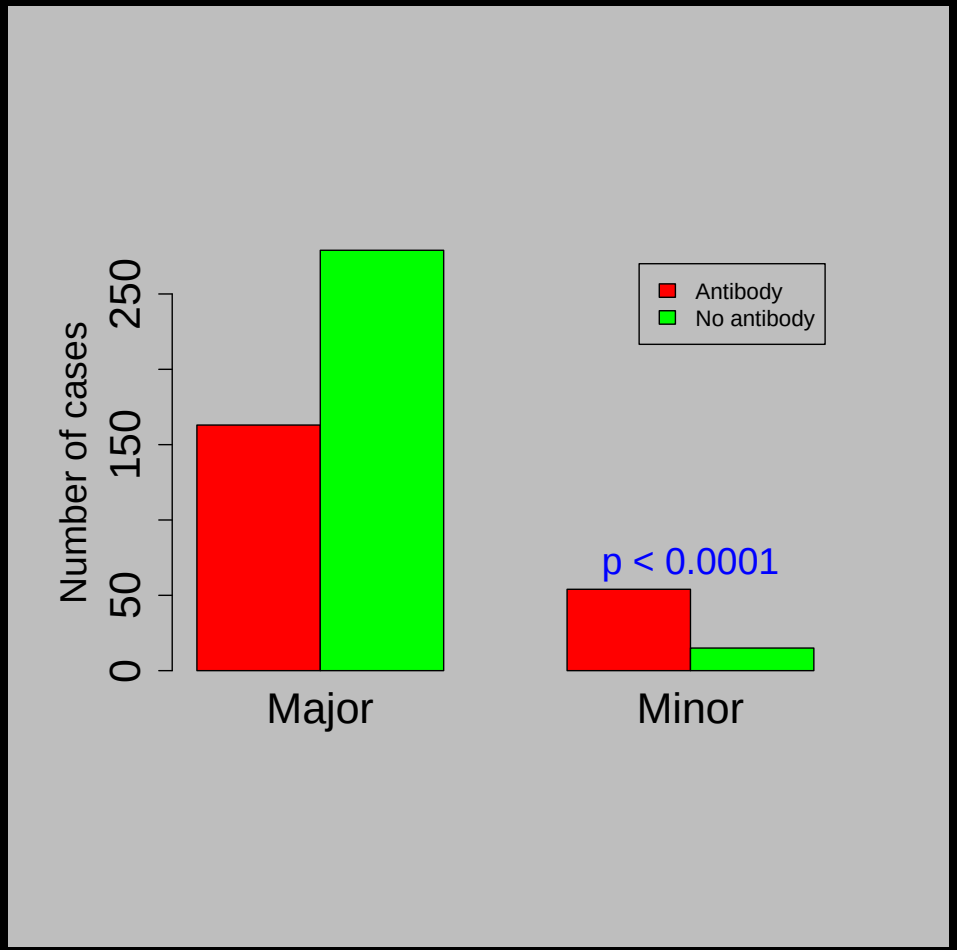
- Although they cannot infect white blood cells, viral attachment makes these cells less quick to move to the lymph node and more likely to produce IL-10
- Minor group viruses attach to members of the Low Density Lipoprotein receptor family, which are not known to have these effects

Kirchberger, 2007

# Minor group induce more immunity




Major group viruses induce immunity in a minority of patients, minor group viruses induce immunity in a majority of patients. Fox, 1985

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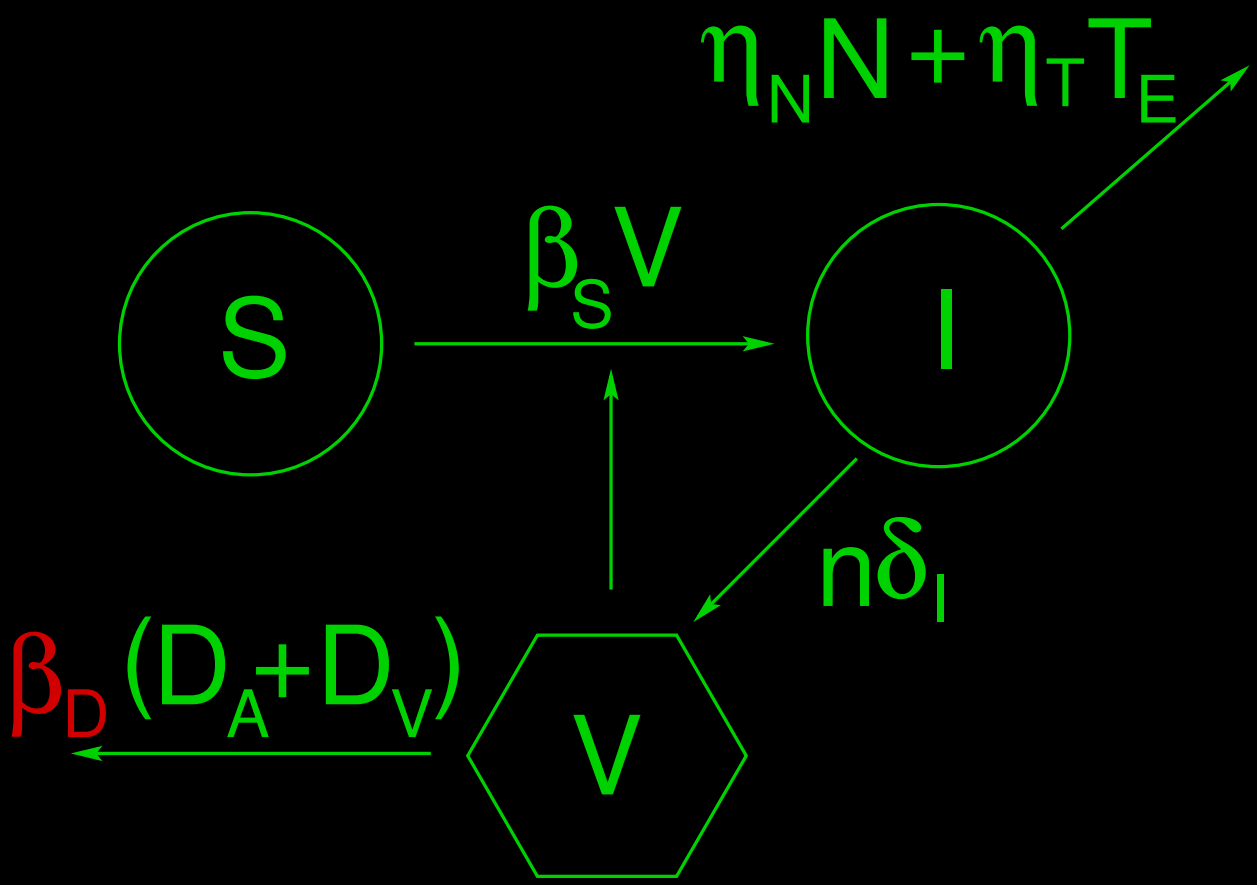
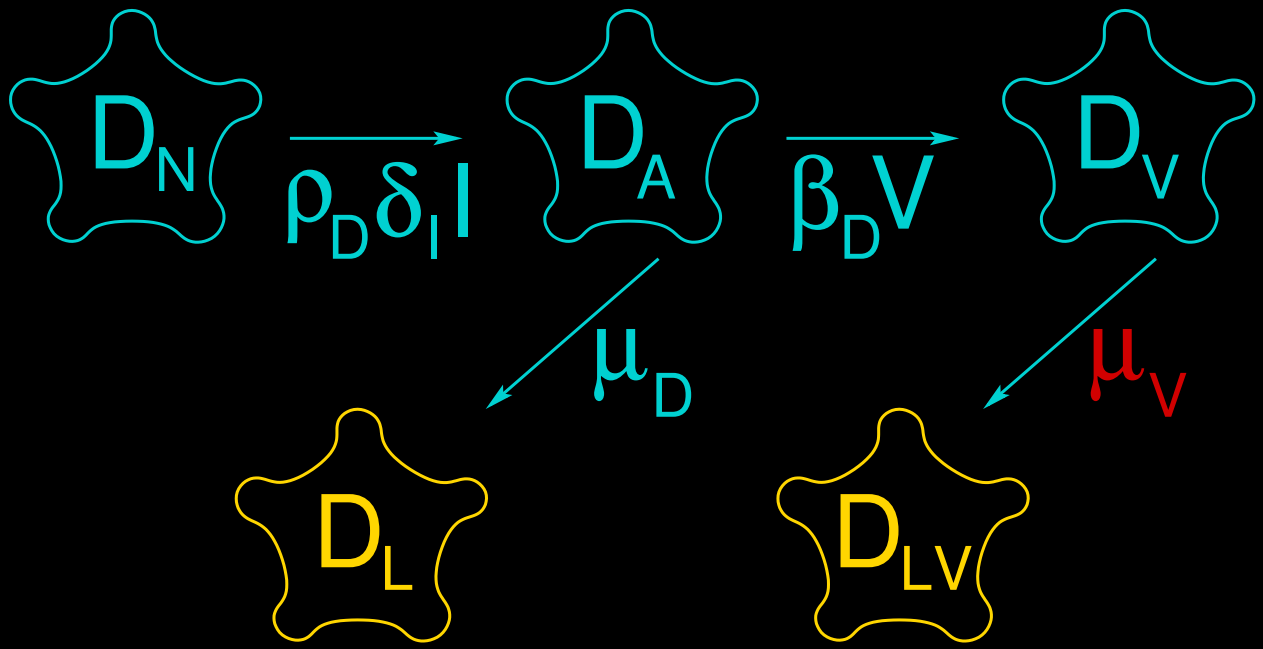
- Antigen Presenting Cells
  1. Delayed in periphery
  2. May arrive in lymph node in a tolerogenic state
- APC produced IL-12
  1. In periphery, activates NK cells to produce IFN-$\gamma$
  2. In lymph node, activates appropriate Th1 response

# The viral dynamics module



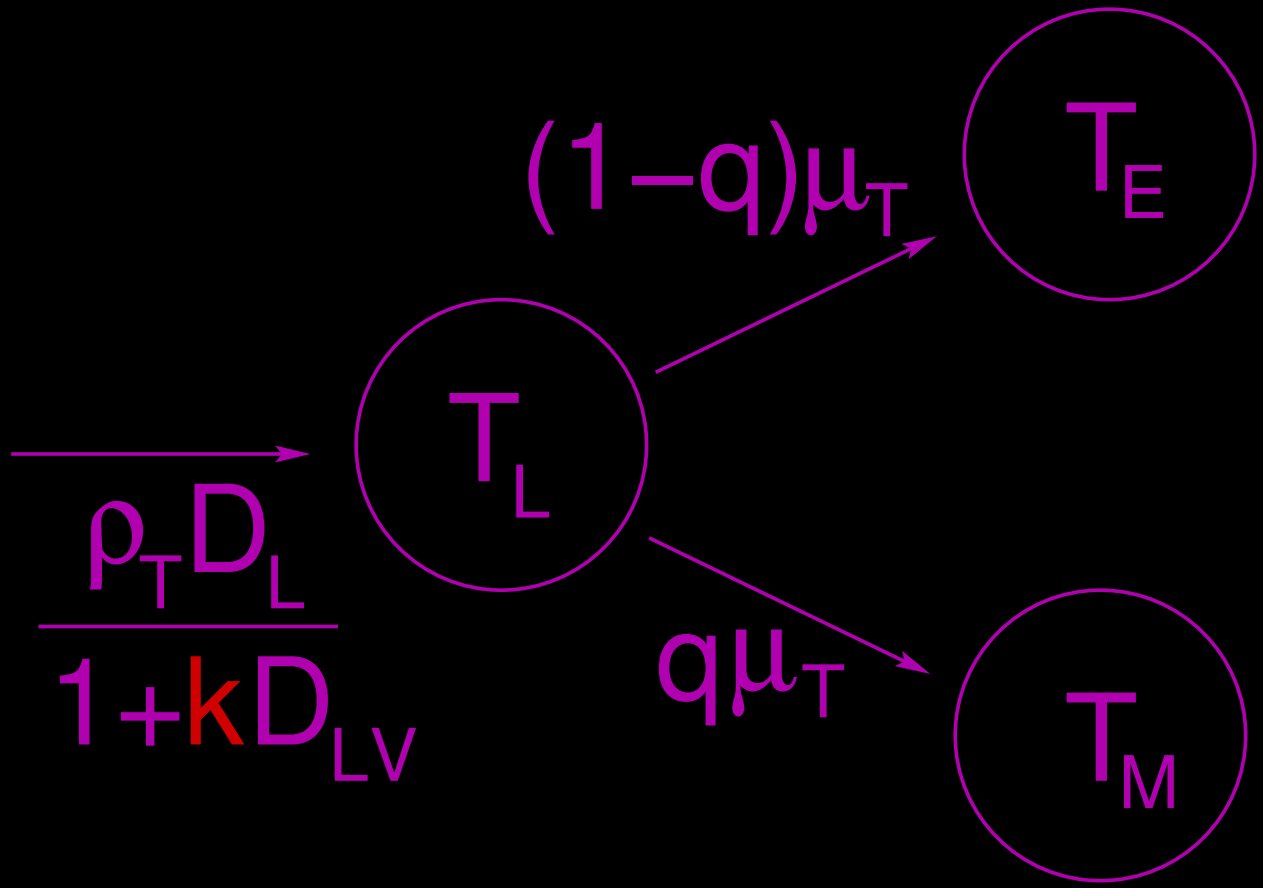

- V is free virus, S susceptible cells, I infected cells
- $D_A$ and $D_V$ are activated and virally-bound dendritic cells
- N and $T_E$ are natural killer and effector T-cells

# The dendritic cell module




- $D_N$, $D_A$ and $D_V$ are naive, activated and virally-bound dendritic cells in the periphery
- $D_L$, and $D_{LV}$ are unbound and virally-bound dendritic cells in the lymph node

# The T-cell module




- $T_L$, $T_E$ and $T_M$ are activated, effector and memory T cells
- $k$ describes how virally-bound dendritic cells inhibit a T cell response in the lymph node

# Parameters...

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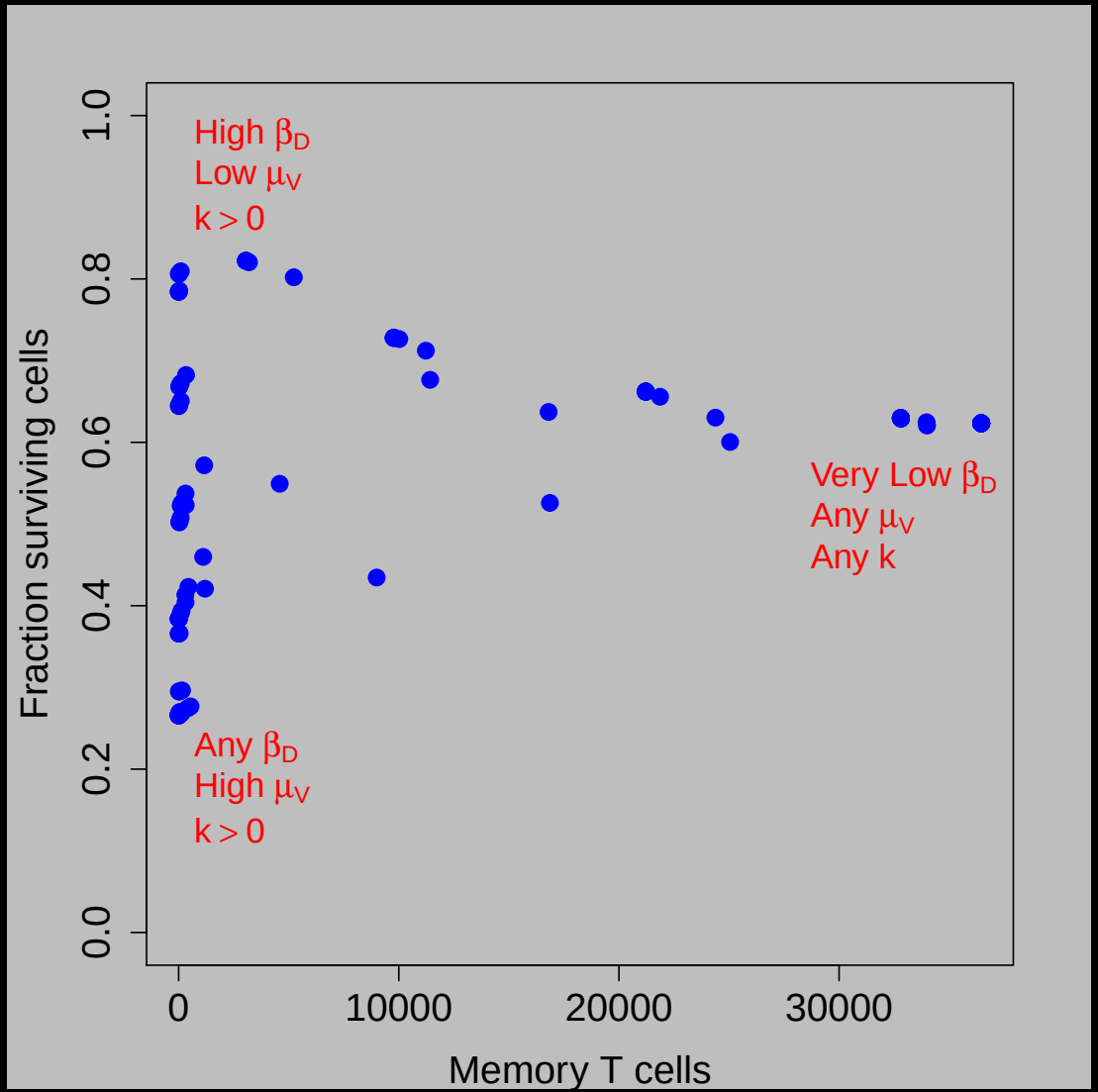
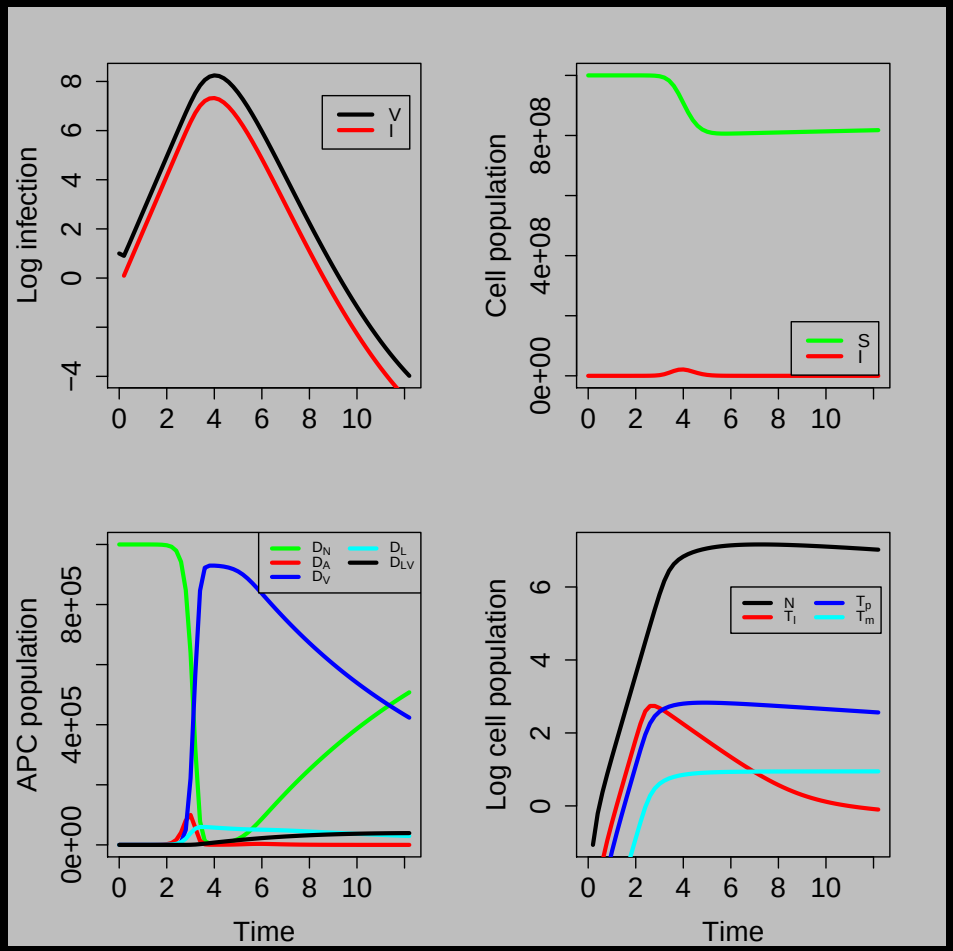
- Can estimate all of the rate constants to within an order of magnitude
- Use an internal $R_0$ of about 10 to get some binding rates
- Experiment with the key parameters $\beta_D$, $\mu_V$ and $k$ that describe virus binding to dendritic cells, interference with dendritic cell migration to the lymph node, and interference with the T cell response

# Does it work?


High $\beta_D$
Low $\mu_V$
k > 0
Very Low $\beta_D$
Any $\mu_V$
Any k
Any $\beta_D$
High $\mu_V$
k > 0
Fraction surviving cells
0.0
0.2
0.4
0.6
0.8
1.0
0
10000
20000
30000
Memory T cells

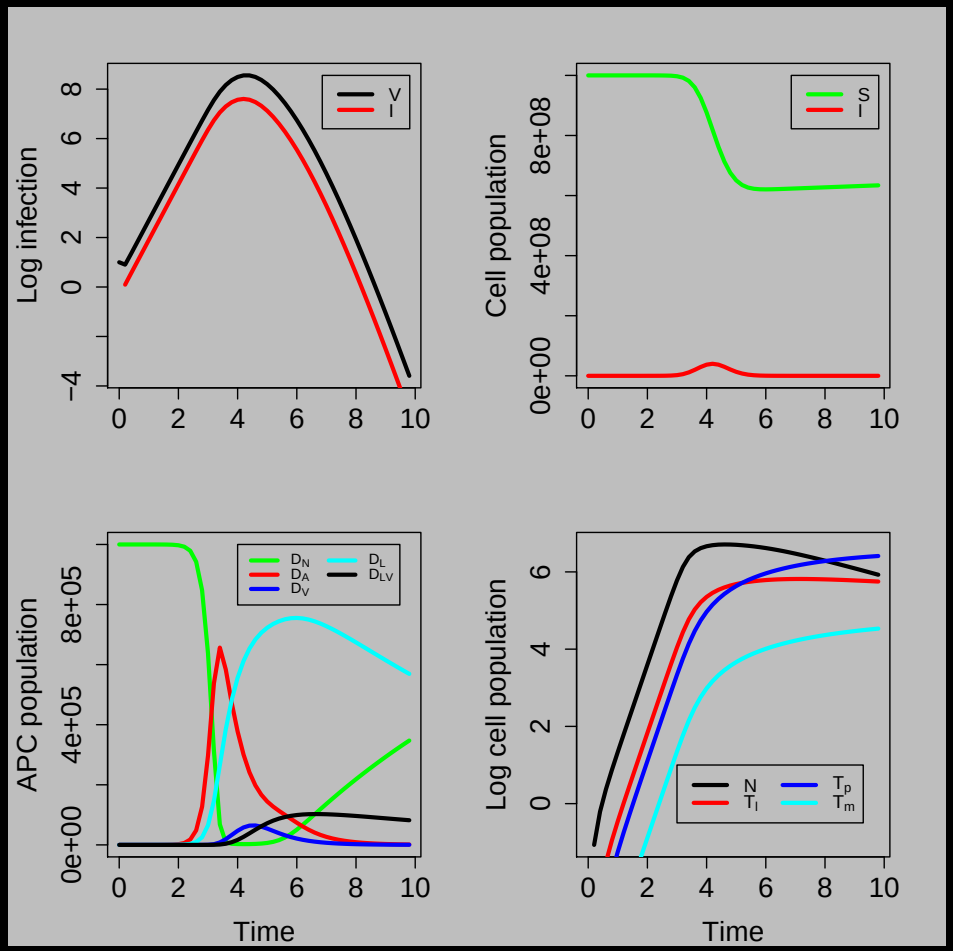
# Dynamics in the low memory case

When viruses stick to dendritic cells, slow their movement, and interfere with T cell activation, get low damage and almost no memory.



# Dynamics in the high memory case

When viruses do not stick to dendritic cells, get moderate damage and high memory.



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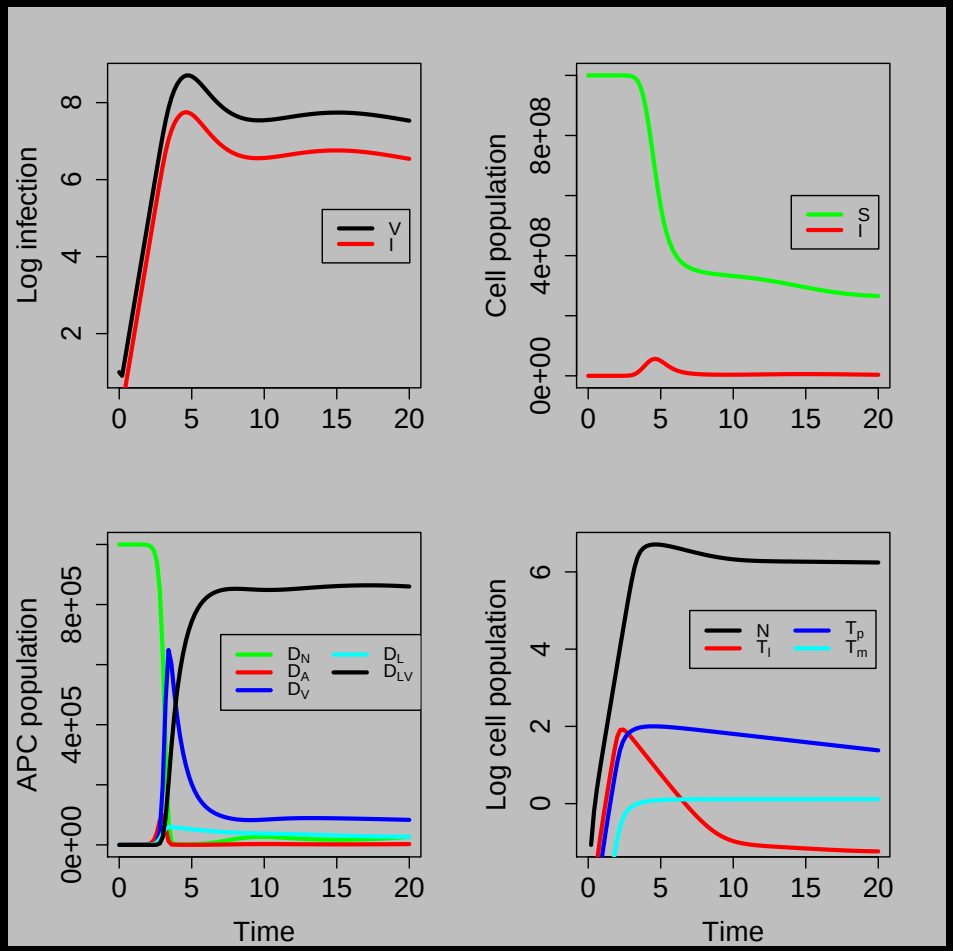

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- Model the interaction of immune dynamics with the evolution of diversity and immune escape
- Evaluate the possible importance of coinfection in maintaining the minor group viruses as "cheaters" that hijack the ability of Major group viruses to suppress the immune response
- Use new genetic and epidemiological data to refine these models and hypotheses

# Acknowledgments


- William Koppelman
- Brendan O'Fallon
- Jon Seger
- Wayne Potts
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* No computers were mistreated by the use of Microsoft products in creating this talk